Assessment of Diagnostic Criteria for Acute Fatty Liver of Pregnancy

A dissertation submitted to the

Tamil Nadu Dr. MGR Medical University,

Chennai

Doctor of Medicine (D.M)

Branch IV

(Gastroenterology)

August 2009

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August 2009

Certificate

This is to certify that this dissertation entitled ‘Assessment of Diagnostic Criteria for Acute Fatty Liver of Pregnancy’ is a bonafide work done by Dr. Ashish Goel in partial fulfillment of rules and regulations for DM (Branch IV-Gastroenterology) examination of the Tamil Nadu Dr. MGR Medical University, to be held in August 2009.

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Abstract

Background:

Acute fatty liver of pregnancy is a rare condition and there has been no attempt to correlate clinical diagnostic criteria and histologically proven acute fatty liver of pregnancy (AFLP). The aim of this study was to assess the accuracy of the recommended criteria in diagnosing acute fatty liver of pregnancy that was proven by histology.

Methods:

A retrospective study of patients with acute liver failure in the third trimester of pregnancy was conducted. The patient group included all the patients who had undergone a liver biopsy for a suspicion of pregnancy related liver dysfunction between 1998 and 2008 and an additional group of patients in whom there was another defined cause of acute liver failure in whom no biopsy was attempted. Liver histology was reviewed by a single hepato-pathologist. The patients were classified into three groups – Group A - those in whom the liver biopsy proved that the condition was AFLP, Group B - those in whom the liver biopsy was indeterminate or inconsistent and Group C - those in whom an alternate explanation for liver failure was defined by tests other than biopsy. We tested the accepted clinical criteria for diagnosis in these three groups.

Results:

There were 17 patients in Group A, 7 patients in Group B and 11 patients in Group C. Using Group A and C to measure sensitivity and specificity we found that the diagnostic criteria

were 100% sensitive but had a low specificity. The criteria were also positive in a proportion of the small number of cases in Group B – the indeterminate group.

Conclusion:

The diagnostic criteria are an accurate way of diagnosing acute fatty liver of pregnancy with a 100% negative predictive value. Therefore these criteria are useful in making the diagnosis but do not exclude other causes, which must always be scrupulously excluded.

Key words:

Acute fatty liver of pregnancy, AFLP, HELLP syndrome, pre-eclampsia.

Introduction

Abnormal liver tests occur in 3%-5% of pregnancies, with many potential causes. Although relatively uncommon, any liver disease can occur coincidentally in the pregnant patient and pregnancy may occur in a patient with underlying chronic liver disease. However, most liver dysfunction in pregnancy is pregnancy-related and due to one of the 5 liver diseases unique to the pregnant state—hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy (ICP), pre-eclampsia, HELLP syndrome, and acute fatty liver of pregnancy (AFLP)[1].

These conditions are associated with pregnancy itself, and each has a characteristic timing in relation to the trimesters of pregnancy: HG in the first trimester, ICP in the second half of pregnancy, and the other 3 in the third trimester.

Other rare conditions that occur more commonly during pregnancy are - Budd- Chiari syndrome, hepatic haematoma and rupture, hepatic infarction and primary hepatic malignancy[2]. Common causes in each group are listed in Table 1.

Of all pregnancy related liver diseases, pre-eclamptic liver dysfunction, HELLP syndrome and AFLP are the life threatening causes of liver failure. There is a considerable overlap in the clinical presentation of these syndromes.

Acute fatty liver of pregnancy (AFLP) is a relatively rare and incompletely understood illness, occurring in 3rd trimester and causing considerable maternal and perinatal mortality. The delay in diagnosis, due to the initial non-specific symptoms, should be avoided. Early termination of pregnancy results in rapid resolution of the illness and so timely diagnosis is of primary importance. The gold standard for diagnosis of AFLP is liver biopsy, which is difficult in an

acute setting[3]. The diagnosis is usually based on clinical criteria which has been proposed by Ch'ng et al[4], and has been recently validated prospectively by Knight et al[5]. None of these studies had liver biopsy as a pre-requisite.

AFLP has only very rarely been reported from India, and the exact incidence or prevalence in Indian population is not known[6-9].

The present study was conducted to evaluate the accuracy of the diagnostic criteria proposed by Ch'ng et al (Swansea criteria) to diagnose biopsy proven acute fatty liver of pregnancy. The clinical features, laboratory and histology parameters and outcome of patients with AFLP were also studied.

Coincidental to pregnancy	**Underlying chronic liver disease**	**Diseases unique to pregnancy**
Viral Hepatitis	Chronic Hepatitis B/ C	Hyperemesis gravidarum,
Gall stones	Auto-immune hepatitis	Intrahepatic cholestasis of pregnancy (ICP),
Drugs	Primary sclerosing cholangitis	Pre-eclampsia,
Sepsis	Wilson Disease	HELLP syndrome
Budd Chiari Syndrome	Primary biliary cirrhosis	Acute fatty liver of pregnancy (AFLP)
	Cirrhosis	

Table 1: Diagnostic categories of liver disease in pregnancy[1]

Aim

1. To assess the accuracy of Swansea criteria for acute fatty liver of pregnancy in diagnosing biopsy proven acute fatty liver of pregnancy.

2. Case series of acute fatty liver of pregnancy with detailed description of clinical features, laboratory parameters, histology findings and outcome.

Review of literature

History :

Acute fatty liver of pregnancy (AFLP) is a maternal liver disease unique to pregnancy. It was first described in 1934 as "yellow acute atrophy of the liver"[10] and was described as a specific clinical entity in 1940[11]. Since then there has been detailed research with description of the histology features and probable pathogenetic mechanisms involved.

The research has been hampered with relative rarity of the disease and especially from India where even large series on acute liver failure in pregnancy, has not identified it as a major cause of the illness[12,13].

Epidemiology of AFLP :

The epidemiologic studies are hampered by the rarity of the condition and the estimate of incidence and prevalence varies depending on the study design. Existing literature consists predominantly of small hospital-based case series or historical cohorts identified retrospectively over a number of years[14,15]. Both these study types have limitations and thus the incidence estimates from these studies vary widely between 1 in 900 and 1 in 16 000 deliveries[4,7,16]. A recent prospective study in UK derived a population based incidence of 1 in 20,000 births[5]. Indian data is scarce but a prospective hospital based study by Rathi et al, estimated an incidence of ~ 1 in 4000 deliveries[7].

It affects women of all ages and races and there is no distinctive epidemiologic feature that has been related to geographic areas or ethnic groups[3]. The onset of AFLP is between the

30th and 38th wk of gestation although an early occurrence at 26 wk has been reported. There are rare reports of AFLP diagnosis in the second trimester[17]. It is more frequent in primaparous than multiparous women but can occur even after multiple uneventful pregnancies. Several reports have documented recurrence of AFLP in subsequent pregnancies[18].

Maternal case fatality estimates range between 12% and 18%, and neonatal mortality estimates range from 7% to 58%[5]. Indian study by Devarbhavi et al, demonstrated a maternal and perinatal mortality of 41% and 53% respectively in patients with pregnancy related liver disease[9].

Pathogenesis of AFLP[3] :

The pathogenesis of AFLP is still elusive and details are still not completely uncovered. Recent molecular advances suggest that it may result from mitochondrial dysfunction, and there has been a strong association between AFLP and deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in the fetus, a disorder of mitochondrial fatty acid beta-oxidation.

Mitochondrial Fatty acid oxidation (Figure 1.[19]) :

The β-oxidation of fatty acids is the major source of energy for skeletal muscle and the heart, while the liver oxidizes fatty acids primarily under the conditions of prolonged fasting, during illness, and at periods of increased muscular activity.

Mitochondrial ß-oxidation of fatty acids is a complex process that consists of multiple transport steps and four enzymatic reactions resulting in the sequential removal of two-carbon, acetyl-coenzyme A units. The 4 reactions in steps in ß-oxidation spiral are demonstrated in Figure 1. Each step has separate sets of enzymes.

For long chain length fatty acids, the last three steps are mediated by an enzyme complex called mitochondrial trifunctional protein (MTP). MTP, also known as trifunctional protein (TFP), is a hetero-octamer of 4α- and 4ß- subunits. The α-subunit amino-terminal domain contains the long chain 3-enoyl-CoA hydratase enzymatic activity while the LCHAD enzymatic activity resides in the carboxy terminal domain. The ß-subunit has the long-chain 3-ketoacyl-CoA thiolase enzymatic activity. Both subunit genes, HADHA and HADHB, have been localized to chromosome 2p23[20].

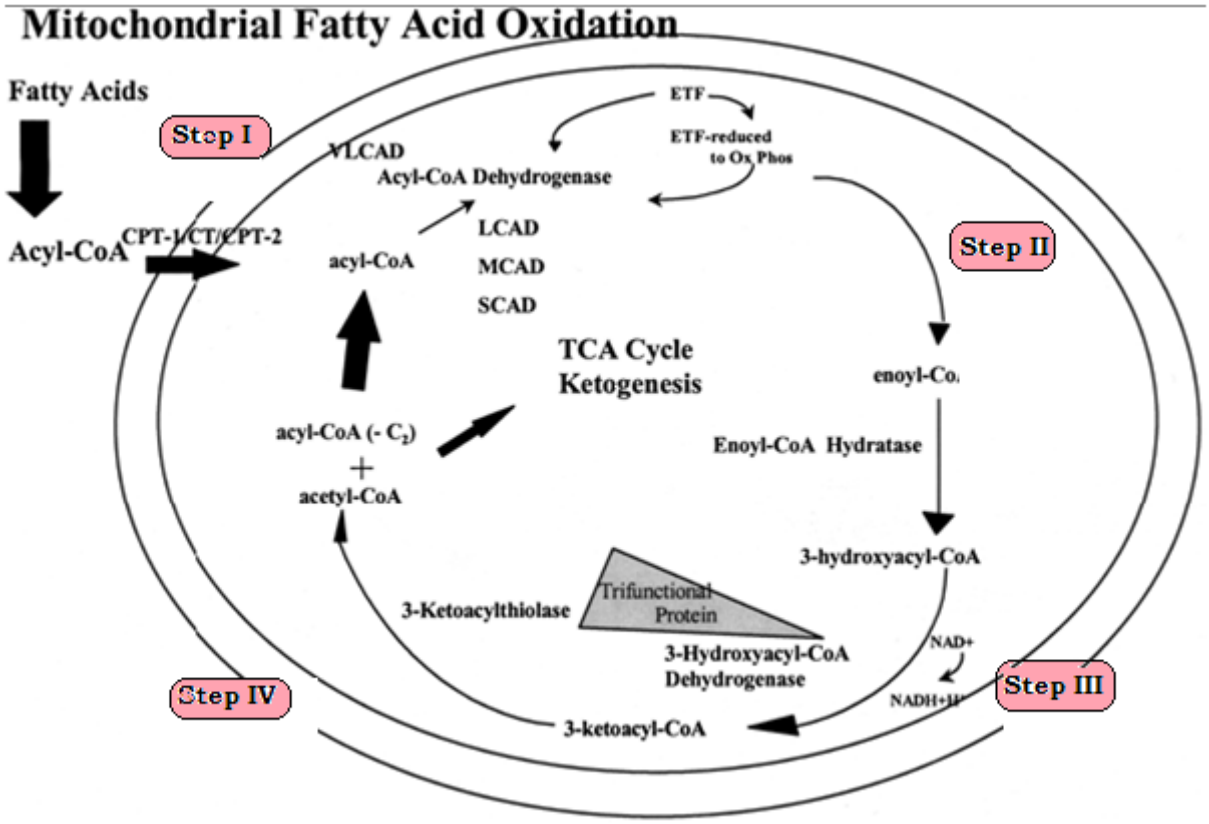

Figure 1: Overview of mitochondrial ß-oxidation of fatty acids.

CPT-1, carnitine palmitoyltransferase-1; CPT-2, carnitine palmitoyltransferase-2; CT, carnitine/acyl-carnitine translocase; ETF, electron transport flavoprotein; LCAD, long-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA dehydrogenase; SCAD, shortchain acyl-CoA dehydrogenase; TCA, tricarboxylic acid cycle; VLCAD, very long-chain acyl-CoA dehydrogenase

Fatty acid oxidation disorders :

Fatty acid oxidation disorders have become an important group of inherited metabolic disorders characterized by a wide array of clinical presentations and as important causes of pediatric morbidity and mortality. LCHAD deficiency was first described in 1989 and MTP

deficiency in 1992. These defects, if unrecognized can be cause of sudden infant death syndrome (SIDS).

Mitochondrial trifunctional protein defects :

Human defects in the MTP complex are recessively inherited and cause either isolated LCHAD deficiency, with normal or partially reduced thiolase and hydratase activity, or complete MTP deficiency with markedly reduced activity of all 3 enzymes. In the literature, the majority of patients reported have been described as having isolated LCHAD deficiency[21].

G1528C mutation in exon 15 of the α-subunit which alters amino acid 474 from glutamic acid to glutamine (E474Q), results in isolated LCHAD deficiency and was strongly associated with AFLP in mothers and the infant were at risk of hypoketotic hypoglycemia and fatty liver[21]. This mutation blocks ß-oxidation and results in accumulation of 3-hydroxy fatty acid metabolites.

Other mutations in the gene caused deficiency of all the three components of MTP and were not associated with AFLP in mothers.

Fetal mitochondrial trifunctional protein defects and maternal liver disease :

Schoeman et al were the first to notice the relationship between fetal fatty acid oxidation disorder and maternal fatty liver of pregnancy[22]. Since then several studies document strong and somewhat unique causative association between fetal MTP defects and AFLP[23,24].

Ibdah et al, in their study on maternal liver disease in infants with MTP defects, concluded that when carrying an LCHAD-deficient fetus, there is a 79% chance that the pregnancy will be complicated by AFLP or HELLP syndrome[21].

In a subsequent study, Yang et al[25] evaluated fetal genotypes and pregnancy outcomes in 83 pregnancies in 35 families with documented pediatric MTP defects. 60% of the mothers carrying

the affected fetuses had AFLP or HELLP syndrome, and all women who had the maternal illness carried fetuses with isolated long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency[25].

Yang et al[26] in another study prospectively screened 27 pregnancies complicated by AFLP and 81 pregnancies complicated by HELLP syndrome. Out of the 27 women that developed AFLP, 5 carried fetuses with MTP mutations. Three were homozygous for the G1528C mutation and two were compound heterozygotes. None of the children born to the 81 women diagnosed with HELLP syndrome carried MTP mutations. This study documents that in approximately one of five pregnancies complicated by AFLP, the fetus is LCHAD-deficient.

This strong association between AFLP and the common G1528C mutation in the fetus is significant and hence screening the offspring of women who develop AFLP at birth for this mutation can be life saving. If done early it may identify LCHAD-deficient children before they manifest the disease allowing early dietary intervention by institution of a diet low in fat, high in carbohydrate, and by substitution of the long chain fatty acids with medium chain fatty acids. In addition, it allows genetic counseling for the mothers and prenatal diagnosis in subsequent pregnancies, which was shown by Ibdah et al as feasible and useful[27].

Possible hypothesis for the association between fetal LCHAD deficiency and acute fatty liver of pregnancy :

The precise mechanism by which an LCHAD-deficient fetus causes AFLP in a heterozygote mother is still unclear. The hypothesis is illustrated in Figure 2. The heterozygosity of the mother reduces her capacity to oxidize long chain fatty acids. Also there is an increased lipolysis and decreased oxidation during stressful conditions- e.g. pregnancy. In the presence of

the G1528C mutation, potentially hepatotoxic long chain 3-hydroxyacyl fatty acid metabolites, produced by the fetus or placenta[28], accumulate in the maternal circulation.

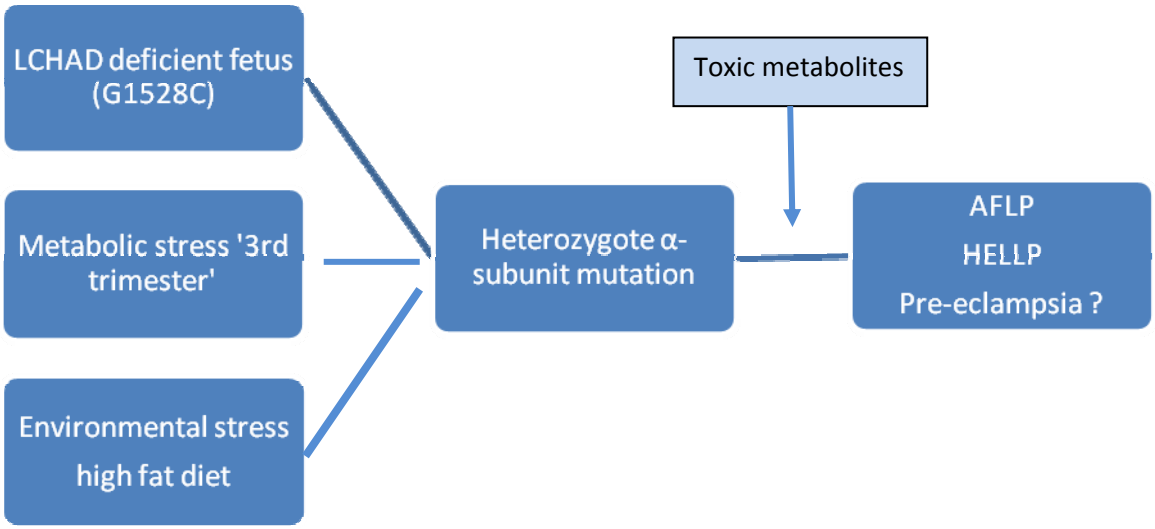

Figure 2 : Hypothesis illustrating the possible role of fetal and maternal MTP mutations in developing acute fatty liver of pregnancy[3].

The role of other fatty acid oxidation defects in development of AFLP is not very clear. There have been case reports linking AFLP like disease in mother to fetal deficiency of carnitine palmitoyl transferase I (CPT-I)[29], SCAD[30], and MCAD[31].

Long chain defects were 50 times more likely than controls to develop maternal liver disease and short and medium chain defects were 12 times more likely to develop maternal liver disease[32].

To conclude, 1 in five patients with AFLP has LCHAD deficiency, emphasizing the importance of genetic testing in these patients and their off springs. It also highlights that 80% of the patients with AFLP do not have a known cause, and further research is needed to elucidate the other possible pathogenetic mechanisms.

Clinical features of AFLP[1,2,3,5,7] :

40%-50% of patients with AFLP are nulliparous, with an increased incidence in twin pregnancies[32,33]. AFLP occurs almost exclusively in the third trimester and very rarely in late second trimester. In a few patients, it presents as jaundice in the postpartum period.

The presentation can vary from asymptomatic to fulminant liver failure. The typical patient has 1 to 2 weeks of anorexia, nausea and vomiting, headache, and right upper quadrant pain, and is ill-looking with jaundice, hypertension, edema, ascites, a small liver, and hepatic encephalopathy. Polydipsia and skin pruritus were the unusual symptoms[16,34]. AFLP patients may also present with upper gastrointestinal hemorrhage (due to portal hypertension and coagulation abnormalities), acute renal failure, sepsis, pancreatitis, hypoglycemia or metabolic acidosis. Hepatic encephalopathy tends to occur late in the disease[2].

Intrauterine death may occur. About 50% of patients with AFLP have preeclampsia, and there is some overlap with the HELLP syndrome[35].

The initial clinical features are thus very non-specific and it needs a high index of clinical suspicion to arrive at an early diagnosis.

Laboratory and radiologic features of AFLP :

The features are non-specific and do not help reach a confirmatory diagnosis. Aminotransferases vary from near normal to 1000, usually 300- 500 IU/L; bilirubin is usually less than 5 mg% but higher in severe or complicated disease. Serum alkaline phosphatase levels are mildly elevated but can be as high as 3-4 times normal.

Other typical abnormalities are normochromic, normocytic anemia, high white blood cell count, normal to low platelets, coagulopathy with or without DIC, metabolic acidosis, renal dysfunction (often progressing to oliguric renal failure), hypoglycemia, high ammonia, hyperuricemia and biochemical pancreatitis[1,2,32]. In comparison with those with HELLP syndrome, patients with AFLP are more likely to show liver failure with coagulopathy, hypoglycemia, encephalopathy, DIC, and renal failure[1,2,5,34,36].

Ultrasound, computerized tomography and magnetic resonance imaging have been

utilized as non-invasive tools for diagnosing AFLP but their value remains limited with false negative results being most common. Ultrasound revealed ascites and/or bright liver in only a quarter of patients in the prospective study by Knight et al[5].A study revealed that computed tomography findings were normal in > 50% of patients with AFLP[37]. Thus in clinical practice, the decision to deliver the fetus should not be delayed by the time required to obtain or the results of these radiologic examinations[2,37].

Pathology of AFLP[1,2,38] :

The presumptive diagnosis of AFLP is made on compatible clinical and laboratory features, the need for expeditious therapy and presence of coagulopathy precludes biopsy.

A definitive diagnosis is histological—micro vesicular fatty infiltration (free fatty acids) predominantly in zones 2 and 3 with lobular disarray and only a mild portal inflammation with cholestasis[39,40,41].

Fatty metamorphosis demonstrated as cytoplasmic ballooning (fat droplets <1 μm), discrete micro vesicles (2-12 μm); and/ or macro vesicles was the dominant change in the biopsy/autopsy specimens of acute fatty liver of pregnancy, in a study by Rolfes et al[38]. These represented a continuum of change with ballooning being present early in the course of the disease. Similarly late in the convalescent phase, ballooning may represent mobilization of fat from the liver. Ballooning usually represents micro droplets of lipid which are not visible on light microscopy, and so an alternative fat stain may be helpful. Fatty metamorphosis may be zonal or pan-acinar.

The other features noted in this study were – hepatocyte necrosis, mild to moderate cholestasis, minimal or no inflammation, extramedullary hematopoiesis and absence of fibrosis.

Substantial loss of parenchyma is responsible for small size of liver, and prolapse of hepatocytes, secondary to necrotizing phlebitis, into hepatic venules leads to portal hypertension.

The histology can be confused with acute viral hepatitis, more so early in the disease, and also with pre-eclampsia in rare cases[42].

Electron microscopy: In patients with cytoplasmic ballooning, non-membrane bound lipid droplets were demonstrated in the patients lacking micro vesicular steatosis on light microscopy. Mitochondrial abnormalities were also noticed in a minority.

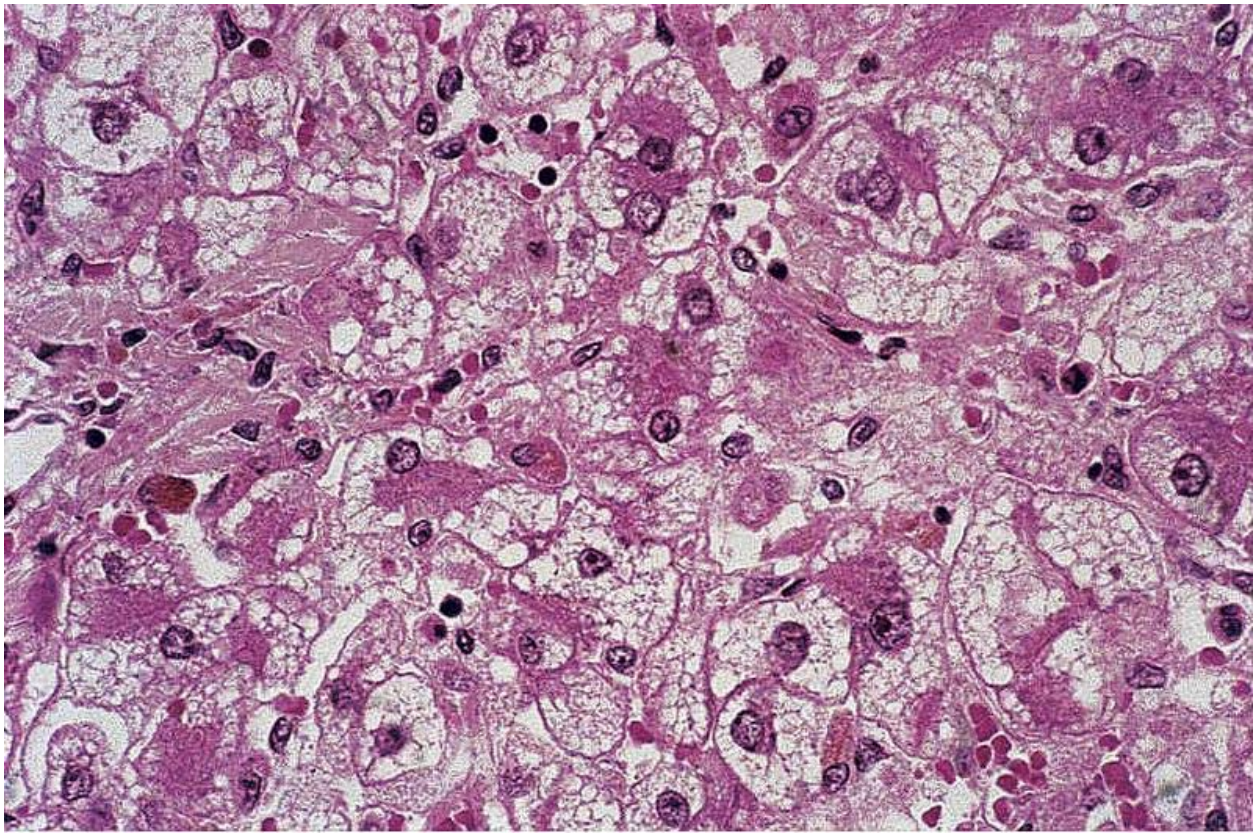

Figure 3. : Slide showing typical features of acute fatty liver of pregnancy- diffuse micro vesicular steatosis and ballooning (H&E stain).

Diagnosis of AFLP :

The initial presentation of AFLP is usually non-specific. The symptoms, signs and laboratory features are not specific enough to diagnose or rule out the possibility of AFLP. The radiologic features are also usually not helpful in this aspect. Histology, though is supposed to be gold standard, is difficult to obtain in a sick patient with coagulaopathy and ascites[1,2,3]. Thus the diagnosis of acute failure of pregnancy is essentially one of exclusion. It should be suspected in

any patient with jaundice with or without acute liver failure in 3rd trimester with no etiology evident. The difficulty is in obtaining an etiologic workup at the earliest; esp. in lesser equipped centers[9].

Ch'ng et al[4] in their study proposed a set of diagnostic criteria for AFLP. The criteria proposed were based on the prior retrospective case series on the subject[41,43,44]. These criteria were recently validated in a large prospective study by Knight et al[5]. These criteria known as 'Swansea criteria', lay down a list of parameters for the diagnosis of various pregnancy related liver diseases. These are shown in Table 2.

These criteria are a mix of various parameters and assume the absence of a contributory etiology. Swansea criteria were validated in a recent population based study by Knight et al, and the criteria agreed to the clinical diagnosis of the physician. There was no gold standard for the diagnosis in this study and it showed only an agreement between clinical judgment and Swansea criteria. There has been no study evaluating the accuracy of these criteria against gold standard – liver biopsy.

Secondly, the assumption of negative etiology workup is an important drawback. These set of criteria cannot distinguish other etiology of liver failure from AFLP and thus may not be helpful in making a decision in emergency setting in a lesser equipped center where a diagnostic workup may take time. Till date there has been no study in demonstrating the usefulness of these criteria in distinguishing AFLP from other etiologies of ALF in pregnancy.

AFLP	Six or more of the following features in the absence of another explanation: • Vomiting • Abdominal pain • Polydipsia/polyuria • Encephalopathy • Elevated bilirubin • Hypoglycemia • Elevated urate • Leucocytosis • Ascites or bright liver on ultrasound scan (USS) • Elevated transaminases • Elevated ammonia • Renal impairment • Coagulopathy • Micro vesicular steatosis on liver biopsy
HELLP syndrome	• Elevated AST >70 iu/l • Low platelet count $100X10^9$/l • Hemolysis (lactate dehydrogenase (LDH) >600 U/l).
Partial HELLP syndrome	• Elevated AST > 40 iu/l • Low platelet count $<150X10^9$/l • Absence or presence of hemolysis.
Pre-eclamptic liver dysfunction	Elevated liver enzymes or bilirubin in the presence of hypertension, proteinuria, and edema after 20 weeks of gestation.
Hyperemesis gravidarum	Elevated liver enzymes or bilirubin in the presence of persistent vomiting for more than one week during the first or second trimester.
Obstetric cholestasis	Pruritus with elevated serum transaminases and/or bile acids in the second or third trimester.

Table 2. : Diagnostic criteria for various pregnancy related liver diseases[4].

Differential Diagnosis :

The patient usually presents with jaundice with/ without liver failure in 3rd trimester. The differentials to be considered are varied – pregnancy in a patient with pre-existing liver disease, incidental liver diseases during pregnancy and pregnancy related liver diseases. The various common conditions in these broad differentials is listed in Table 1.

The history, physical examination, radiologic tests and laboratory parameters usually help in diagnosis of an underlying pre-existent chronic liver disease. The other tests- serology for HAV, HEV, HBV, HCV, CMV; peripheral smear for malaria parasite, USG for choledocholithiasis/hepatic infarct and serology for scrub typhus/ leptospirosis; are done as clinically indicated to differentiate incidental acute liver dysfunction during pregnancy.

The major other condition that must be excluded is the HELLP syndrome, which is characterized by hemolysis, elevated liver enzymes, and a low platelet count. The patients of HELLP usually have only mild elevation of liver enzymes, mild hyperbilirubinemia, no DIC/ coagulaopthy, normal USG and non-specific liver histology. Moreover patients with HELLP are less likely to have the mutatations in fatty acid oxidation pathways[26]. A large clinical overlap between AFLP and HELLP syndrome makes it difficult, even impossible, to differentiate them. However, evidence of hepatic insufficiency such as hypoglycemia or encephalopathy is suggestive of AFLP.

In one series of 46 women who developed liver disease during pregnancy severe enough to require admission to a liver failure unit, 70% had acute fatty liver and 15% had HELLP syndrome[45]. In the study by Rathi et al[7], the majority of patients with liver dysfunction in 3rd

trimester were secondary to HELLP/ partial HELLP syndrome. There is a considerable overlap between these syndromes and it is often difficult to distinguish between these[46]. The different features of the various pregnancy related liver disease is given in Table 3. There is also a considerable overlap between pre-eclampsia and AFLP as well, but the pathogenetic mechanisms, and histology features are different.

The differentiation between various pregnancy related liver diseases is of theoretic importance only, as the management is singular – prompt termination of pregnancy.

Disorder	Gestational age at presentation	Symptoms	Specific labs	Outcome	Treatment
HG	1st trimester	Nausea and vomiting.	AST,ALT < 200	Benign for mother and child; Likely recurs	IV fluids Thiamine Pyridoxine Promethazine: FDA C
AFLP	3rd trimester	Nausea vomit abdominal pain Progress quickly to FHF, 50% have eclampsia	AST,ALT >300 Bilirubin high DIC Uric acid high	Maternal mortality 30%, Fetal mortality up to 35%. Recurs	Prompt delivery Liver transplant if FHF
IHCP	3rd trimester	Pruritus	GGT≥ normal Bile Acids high PT normal Bilirubin ≤ 5 AST,ALT<300	Increase maternal gallstones related disorders Risk for fetal distress+ Often recurs	Actigall Delivery when fetal distress is imminent
HELLP	Beyond 22 weeks and after delivery.	Abdominal pain Mild renal failure 20% progress from eclampsia	Platelets <100,000 Hemolysis, DIC	Maternal mortality up to 3.5% and fetal death 6-37 % Hepatic rupture is associated with 60% maternal mortality Likely recurs	Prompt delivery

Table 3. : Features of liver disease unique to pregnancy

Management of AFLP :

The primary treatment of acute fatty liver of pregnancy is prompt delivery, usually emergently, after maternal stabilization. There are no reports of recovery before delivery[1].

Delivery is affected usually by caesarean section, but the type of delivery should be based on obstetric assessment of likelihood of rapid controlled vaginal delivery in less than 24 hours. Vaginal delivery will reduce the incidence of major intra-abdominal bleeding but is best affected with an international normalized ratio of less than 1.5 and platelet count of greater than 50,000[1]. Prophylactic antibiotics are recommended to prevent uterine infections[1,32].

The prothrombin time usually starts to normalize shortly thereafter although, in most severe cases, there may be many more days of illness requiring maximal supportive management in an intensive care unit, including mechanical ventilation because of coma, dialysis for acute renal failure, parenteral nutrition because of associated pancreatitis, or even surgery to treat bleeding from a preceding cesarean section.

Maternal stabilization requires glucose infusion and reversal of coagulopathy (e.g., administration of fresh frozen plasma, cryoprecipitate, packed red blood cells, and, rarely, platelets), as needed. Attention should be paid to the women's overall fluid status; therefore, small volumes of cryoprecipitate are often preferable to fresh frozen plasma. Antibiotics prophylaxis is to be strongly considered.

Most severely ill patients recover and have no sequel of the liver disease itself[47]. However, substantial morbidity and mortality can occur. In a population-based study that included 57 patients with acute fatty liver of pregnancy, one woman required a liver transplant and one woman died (case fatality rate of 1.8 percent, 95% CI 0 to 9 percent)[5]. There were seven deaths among 67 infants (perinatal mortality rate of 104 per 1000 births, 95% CI 32 to 203). Other

reports have also described patients who required liver transplantation[48,49] but it is unlikely to be needed with early diagnosis and prompt delivery.

Prognosis and Outcome in patients with AFLP:

Recovery can occur in days or be delayed for months but is complete with no signs of chronic liver disease[1].

With advances in supportive management of these patients, the mortality is reduced from almost universal to – maternal being 7%-18% and fetal mortality 9%-23%[1,50].

There have been case reports of the recurrence of AFLP in subsequent pregnancies[18,51], and patients are to be referred to genetics specialist for screening and counseling.

Newborns of these patients may have fatty acid oxidation defect[25-27] and they typically present with hypoketotic hypoglycemia, metabolic acidosis, hepatic failure, and cardiomyopathy. Late presentations include episodic myopathy, neuropathy, retinopathy, and arrhythmias. Sudden unexpected death can occur at any age and can be confused with sudden infant death syndrome[52].

Regarding the infant, screening for LCHAD deficiency should be performed on all babies born to mothers with a diagnosis of AFLP. Those who are positive for reducing substances in the urine should undergo formal genetic testing. These babies should also be managed with high carbohydrate, low fat diets and not allowed to fast for more than four hours[2,52].

Thus, AFLP represents a rare, treatable and reversible cause of acute liver failure, with prompt and complete recovery after early recognition and emergent delivery.

Materials and Methods

Case finding :

We found the cases by collecting all the patients who underwent liver biopsies for acute liver failure in the third trimester of pregnancy during the period 1998 to 2006. The hospital records of these patients were studied. Data abstracted from the records included the parameters needed for clinical diagnosis, time of admission to hospital, time of delivery of the baby and time of liver biopsy. Patients with incomplete data were excluded.

For negative disease controls, we collected as many cases as we could of those with acute liver failure where a definite etiological agent was discovered by tests other than biopsy. By this we assumed that AFLP was excluded in them.

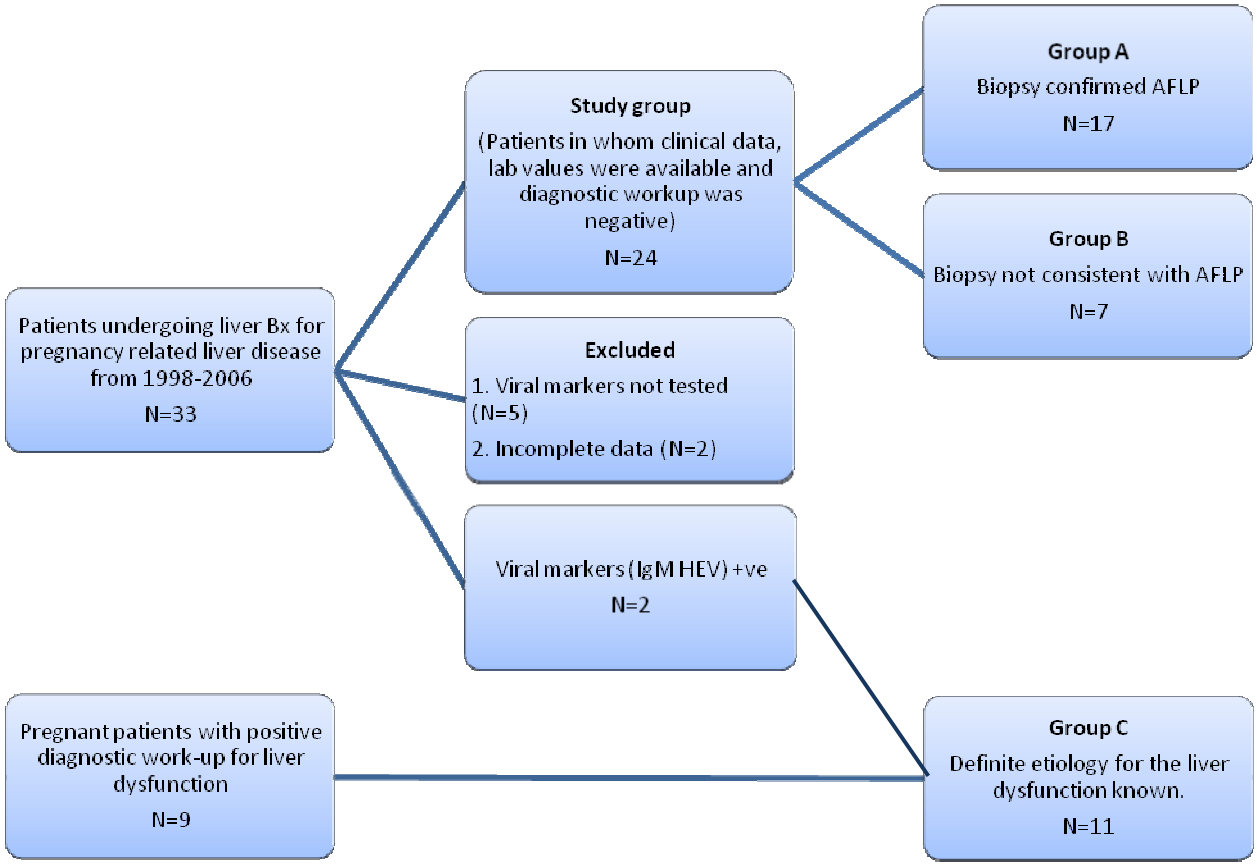

Figure 1. : Flow chart depicting the patients in the various groups of the study.

Methods of classification :

Patients were classified into three groups.

Group A- Those in whom the biopsy was consistent with AFLP. These were patients who had to have a completely negative investigative work-up for other etiologies before liver biopsy was done.

Group B- Those in whom a biopsy was available but the histology was inconsistent with AFLP. These too had a negative pre-biopsy work up.

Group C- Those in whom a pre-biopsy investigative work up identified a cause of acute liver disease making biopsy irrelevant.

Ch'ng et al[4], in their study, have proposed diagnostic criteria ('Swansea criteria') for the pregnancy related liver diseases - HELLP, partial HELLP and pre-eclamptic liver dysfunction besides AFLP. The criteria for AFLP are enumerated in Table 1.

The patients in group A were classified according to these criteria. Patients in group B – where the histology was inconsistent - were also classified by these criteria into AFLP, HELLP, Partial HELLP or pre-eclamptic liver dysfunction. Patients in group C were defined by etiological agents identified by blood tests and any histology available was noted but not used in reaching an etiological conclusion.

AFLP(numbers in parentheses indicate freq. in study group)
Presence of ≥ 6 of the following in absence of alternate explanation : ▪ Vomiting (11/21) ▪ Abdominal pain (3/14) ▪ polydipsia/polyuria (1/1) ▪ Encephalopathy (9/24) ▪ Elevated bilirubin (24/24) ▪ Hypoglycemia (6/20) ▪ Hyperuricemia (8/10) ▪ Leucocytosis (20/23) ▪ Ascites or bright liver on USG* (15/21) ▪ Elevated transaminases (23/24) ▪ Renal impairment (15/24) ▪ Coagulopathy (23/24) ▪ Micro-vesicular steatosis on biopsy (17/24)

'*'- 3 patients had USG after delivery.

Table 1. Proportion of patients in the study group meeting the criteria laid down by Ch'ng et al[4].

Histology :

The biopsies were reviewed by a single hepatopathologist unaware of the diagnosis based on the Swansea criteria and various findings were noted. The biopsies were classified as consistent with acute fatty liver of pregnancy, if it showed diffuse micro-vesicular steatosis with vacuolation and ballooning.

Statistical Methods:

The data was analyzed using SPSS version 15. Non-parametric tests were used to test significance of the continuous variables in between the three groups. Two-tailed Fischer's exact test was utilized to test the significance between discrete variables. Using liver histology as the gold standard for the diagnosis of acute fatty liver of pregnancy, the performance of the clinical diagnostic criteria was assessed in three groups: groups A - where histology was diagnostic, group B - where histology was inconsistent or non diagnostic and group C - where tests other than biopsy defined an alternative diagnosis. The sensitivity and specificity were calculated using standard formulae.

Results

The results are displayed in 2 parts – Initial part pertaining to testing the accuracy of Swansea criteria for AFLP, and the later part giving a detailed description of the study group characteristics.

Testing the accuracy of Swansea criteria

Patients :

Figure 1 illustrates the derivation of the three groups. A total of 33 patients underwent liver biopsy for the clinical indication of pregnancy related liver disease. Patients with incomplete data, or alternative explanation of their clinical syndrome were excluded, and finally, 24 patients constituted the study group (Figure 1.)

The presence and prevalence of various individual elements of the Swansea criteria is depicted in Table 1.

Classification :

Group A: Of these 24 patients, 17 patients had biopsy confirmed acute fatty liver of pregnancy. The clinical features, laboratory parameters, imaging, management and course and outcome in these patients were noted.

Group B : 7/24 patients had an indeterminate histology and constituted Group B. The histology features in these patients are described.

Group C : 11 patients with a defined etiology of liver failure in third trimester of pregnancy, were studied. The group was utilized to calculate the performance of the diagnostic criteria.

Assessing the accuracy of Swansea criteria to diagnose AFLP :

Of the 24 study patients, 17 (71%) had a liver biopsy consistent with AFLP and all these patients fulfilled the clinical diagnostic criteria. These patients constituted Group A.

4/11 control patients (Group C – i.e patients with definite etiology other than AFLP) had the presence of criteria for diagnosis of acute fatty liver of pregnancy. The table for calculation of sensitivity and specificity is shown (Table 2.).

	Swansea criteria satisfied for AFLP	Swansea criteria not satisfied for AFLP	Total
Patients with confirmed AFLP (Group A- Cases)	17	0	17
Patients with definite other etiology (Group C- Controls)	4	7	11
		Total	28

Table 2. : Calculation of sensitivity and specificity of the Swansea criteria vis-à-vis liver biopsy.

With histological confirmation and negative etiological work-up as the gold standard for diagnosis of AFLP, sensitivity and specificity of the clinical diagnostic criteria were thus 100% and 64% respectively. Positive and negative predictive values were 81% and 100% respectively.

Performance of Swansea criteria in Group B :

3/ 7 patients in group B fulfilled the Swansea criteria for the diagnosis of AFLP, but the histology showed only non-specific findings. Thus, of the 20 patients in the study group who fulfilled Swansea criteria for the diagnosis for AFLP, 3 patients had biopsy which was not consistent with the diagnosis.

AFLP being rapidly reversible syndrome after delivery, the histology findings may reverse if there is delay in obtaining a liver biopsy. There was no significant difference in the two groups as far as the delay in liver biopsy is concerned (Group A- 4.4 ± 2.4 days v/s Group B - 5.9 ± 2.8 days; p-value : 0.18).

On analyzing patients with Swansea criteria positive for AFLP (20 patients), there was a trend to non-confirmatory biopsies with increase in the interval between delivery and liver biopsy (> 5 days, 2/9), while biopsies taken <5 days after delivery were more likely to be confirmatory (10/11). This difference also was not significant.

Detailed description of the features in patients with pregnancy related liver disease - study group (N=24)

The second part of the study entailed description of the features in patients with confirmed AFLP (Group A) and possible differences between different groups.

The study group consisted of 24 patients with acute liver failure in 3rd trimester of pregnancy and all etiologic work-up negative. Among them, 5 patients had post-mortem per-cutaneous liver biopsy, and the rest had post–natal biopsies via the trans-jugular route. The trans-jugular liver biopsies were performed as soon as the clinical condition of the patient permitted the procedure.

The median time between delivery and liver biopsy was 4 days (range 1-11 days). The majority (71%) of the study patients had diffuse hepatic micro-vesicular steatosis, consistent with acute fatty liver of pregnancy, and same was true for the complete cohort of 33 patients who underwent liver biopsy. Biopsy findings in the patients are summarized in Table 3.

Based on the criteria proposed by Ch'ng et al[4], there was a considerable overlap between the various syndromes; which is highlighted in Table 4.

Liver biopsy findings	Study Group * N = 24	All patients with pregnancy related disease who underwent liver biopsy* N= 33
Diffuse micro-vesicular steatosis	17 (71%)	25 (76%)
Bridging necrosis	1 (4%)	1 (3%)
Predominant hepatocanalicular cholestasis	2 (8%)	2 (6%)
Congestion with centrilobuar necrosis	2 (8%)	2 (6%)
Predominant cholestasis with mild inflammation	1 (4%)	1 (3%)
Predominant cholestasis with mild micro-vesicular steatosis	-	1 (3%)
Non-specific changes	1 (4%)	1 (3%)

'*' – Number (percentage)

Table 3. : Liver biopsy findings in the study group, and also in all patients who had biopsy for suspected pregnancy related liver disease during 1998- 2006 at Vellore.

Clinical Diagnoses	Number (Percentage)
AFLP	5 (22 %)
AFLP + HELLP/ Partial HELLP	13 (52 %)
AFLP + Preeclampsia + partial HELLP	1 (4%)
AFLP + Pre-eclampsia	1 (4%)
HELLP Syndrome	1 (4 %)
Partial HELLP Syndrome	1 (4 %)
Preeclamptic liver dysfunction	1 (4 %)
Preeclampsia + HELLP	1 (4 %)

Table 4. : Syndromic diagnoses in the study group (n= 24)

Clinical features in patients with confirmed AFLP (Group A; n=17) :

Patients ranged from 20 – 28 yrs (mean - 23 ± 3 years) and the majority -11 (65%) was primigravida. The mean gestational age was 37 weeks (Range 33 – 40 weeks). 3/17 (18%) patients were delivered elsewhere before being referred for further management. 12 of the 14 patients who had delivery at our institute were delivered within the 1st 24 hours and rest within 36 hours, with a median delay of 7 days (Range 1-15 days) from the onset of symptoms.

Apart from jaundice (100%), other common presenting symptoms were pedal edema (65%), bleeding manifestations (41%), encephalopathy (35%), ascites (41%) and vomiting (59%). Less common symptoms were fatigue (18%), polyuria (6%) and polydipsia (6%). Approximately, a quarter of the AFLP patients had hypertension. None of the patients had a prior or a family history of similar liver disease in pregnancy. Fetal distress was noted in 59% (Table 5**).**

		Group A (n=17)	Group B (n=7)	Group C (n=11)	Group A v/s Group B (p-value)	Group A v/s Group C (p-value)
Age of the patient (years)		22.9±2.6	23.3±4.4	27.5±5.4	0.77	0.03
Clinical presentation	**Jaundice**	17	7	11	1.0	1.0
	Vomiting	10	1	7	0.08	1.0
	Polydipsia/ polyuria	1	0	0	1.0	1.0
	Ascites	7	3	5	1.0	1.0
	Pedal edema	11	6	5	0.6	0.4
	Encephalopathy	6	3	2	1.0	0.4
	Bleeding	7	2	1	0.67	0.1
	Fatigue	3	1	0	1.0	0.26
	Fever	7	0	4	0.07	1.0
	Discharge p/v	1	1	0	0.51	1.0
	Seizures	0	1	0	0.29	1.0
	Fetal distress	10	3	2	0.66	0.05
Duration of symptoms (days)		5.9±3.9	4.3±4.9	4.9±3.4	0.21	0.51
Gravida (1/2/3/>3)		11/4/2/0	6/1/0/0	3/4/1/3	0.51	0.28
Weeks of pregnancy		36.9±2.2	32.4±7.1	33.7±2.8	0.26	0.01

Table 5. : Demographics and mode of presentation in different groups of the study

Laboratory parameters and imaging studies in confirmed AFLP patients (Group A; n=17):

The mean values, standard deviation and range of the initial laboratory tests performed is shown in Table 6.

On ultrasound examination, 18% had a normal liver and no ascites, while 53% had ascites, 12% had a fatty liver and 6% had shrunken liver. The various radiological findings are given in Table 7.

Histology in confirmed AFLP patients (Group A; n=17) :

The biopsy findings of all patients are summarized in Table 3.

In 17 patients with confirmed AFLP according to the diagnostic criteria and histology, the biopsy findings besides diffuse/ perivenular micro-vesicular steatosis or ballooning, were - mild hepatocanalicular cholestasis (15/17), foci of extramedullary hematopoiesis (8/17), mild portal and lobular inflammation (16/17), regeneration (7/17), presence of ceroid bodies (5/17) and minimal necrosis (3/17).

Parameters	Group A (mean±SD)	Group B (mean±SD)	Group C (mean±SD)	Group A v/s Group B (p-value)	Group A v/s Group C (p-value)
S. Bilirubin (mg%)	13.0±3.7	12.1±10.4	9.4±8.0	0.099	0.02
Direct Bilirubin (mg%)	10.8±3.4	9.7±9.0	7.4±6.4	0.81	0.02
S. Protein (g%)	5.0±0.9	4.8±0.8	5.6±1.0	0.85	0.19
S. Albumin (g%)	2.1±0.3	2.2±0.3	2.2±0.7	0.49	0.78
AST (U/L)	146.1±89.0	3645±9341	393.7±433.5	0.62	0.55
ALT (U/L)	129.3±76.3	266.7±480.1	238.5±229.4	0.31	0.49
ALP (U/L)	475.9230.3	298.7±164.1	383.6±260.6	0.05	0.29
LDH (U/L)	1166.6±496.2	1454.3±915.3	787.9±319.2	0.49	0.04
PT (seconds)	39.0±26.7	38.76±39.2	31.1±22.5	0.35	0.19
aPTT (seconds)	88.1±49.7	66.1±52.6	63.4±47.0	0.19	0.08
Fibrinogen (mg%)	103.5±18.5	76.9±46.2	198.7±262.1	0.67	0.64
S. Creatinine (mg%)	1.74±0.82	1.7±1.09	1.05±0.34	0.58	0.01
MELD	32.1±6.7	29.6±10.9	23.7±12.1	0.534	0.13
Uric Acid (mg%)	7.0±0.7	7.6±0.4	6.6±7.8	0.17	0.07
Hb (g%)	14.6±19.2	10.7±2.3	9.8±3.0	0.66	0.58
Total count ($x10^3$percmm)	20.2±7.3	19.7±9.3	19.3±8.4	0.92	0.82
Platelets ($x10^5$percmm)	1.24±0.58	0.80±0.57	1.82±0.97	0.08	0.07

Table 6. : Laboratory parameters in patients in different groups

		USG abdomen					Total
		Normal	Ascites	Fatty liver	Volume redistribution	Not done	Normal
Groups	Group A	3	9	2	1	2	17
	Group B	2	4	0	0	1	7
	Group C	5	4	1	0	1	11
Total		10	17	3	1	4	35

Table 7. : Radiological features in different groups of the study.

Course and Outcome in confirmed AFLP patients (Group A; n=17) :

2 (12%) of the mothers and 5 (29%) of the babies had a fatal outcome. The outcome is depicted in Table 8.

The mean stay in hospital was 11 ± 4 days (Range 1- 19 days) and an average of 18 ± 15 blood products were administered per patient. Among the 17 AFLP patients, 9 were delivered by Caesarean section and others by vaginal route. 12/17 babies were male and 3 were twins. The details are shown in Table 9.

Biochemical parameters, mode of delivery, sex of the baby and time delay of delivery from onset of symptoms and from admission did not have any influence on the maternal and fetal outcome in this group of patients.

	Group A	Group B	Group C	Group A v/s Group B (p-value)	Group A v/s Group C (p-value)
Adverse maternal outcome (Death)	2	3	4	0.09	0.12
Adverse fetal outcome (IUD/ Still birth/ Death immediately after birth)	5	3	2	0.59	0.92

Table 8. : Outcome of the patients in different groups of the study.

	Group A	Group B	Group C	Group A v/s Group B (p-value)	Group A v/s Group C (p-value)
Hospital stay (days)	11±4	10±6	13±5	0.95	0.49
Blood products required	18±15	16±19	8±9	0.41	0.06
Mode of delivery (Vaginal/Caesarean)	8/9	4/3	5/3*	-	-
Sex of the child (Male/Female/Twins)	12/2/3	3/4/0	2/2/0*	-	-

'*' – Data not complete

Table 9. : Course of the patients in different groups of the study.

Characteristics of the patients in Group B (n=7) :

Of the 24 study patients, who had no etiology for the acute liver failure, 7 had an histology which was not consistent with acute fatty liver of pregnancy.

The demographics, mode of presentation, laboratory parameters, radiologic features, maternal and child outcome and course are noted in Table 6, Table 7, Table 8, Table 9 and Table 10 respectively. The details of the histology in these patients are noted in Table 2. It was very similar to Group A in all characteristics and final outcome.

Control Group (Group C) :

The control group consisted of 11 patients having jaundice complicating third trimester of pregnancy, with a well defined etiology. The etiology of liver dysfunction in these patients was - acute hepatitis E (6 patients), acute hepatitis A and B (1 patient each), scrub typhus (1 patient), S. paratyphi infection (1 patient) and malaria (1 patient).

The demographics, mode of presentation, laboratory parameters, radiologic features, maternal and child outcome and course are noted in Table 6, Table 7, Table 8, Table 9 and Table 10 respectively. As compared to group A, patients in group C were older, presented earlier in the course of pregnancy and had a lower S. bilirubin and S. Creatinine. The outcome though, was similar in both the groups.

Of these 11 patients, 4 fulfilled the diagnostic criteria for acute fatty liver of pregnancy. These 4 patients, who fulfilled diagnostic criteria, had a significantly higher MELD score (36 v/s 17; p-

value – 0.02), S. bilirubin (16.6 v\s 5.3; p-value 0.01) and prothrombin time (52.5 v/s 18.9; p-value – 0.04). Though not attaining stastical significance, maternal mortality was higher in these 4 patients (2/4; 50%) as compared to the others (2/7; 29%). Thus the diagnostic criteria, if applied to this group of patients, identified a sicker individual.

Discussion

Acute fatty liver of pregnancy is a relatively rare but serious occurrence[1]. The importance of early recognition and timely management of AFLP derives from the improvement in maternal and fetal outcomes with early delivery of the fetus[1,2,3].

There have been only a few case reports pertaining to the disease from this part of the world[6]. Contrary to the recently published data on acute liver failure in pregnancy[13], this case series illustrates the presence of acute fatty liver of pregnancy as an important cause of acute liver failure in pregnancy in south India.

A liver biopsy is considered to be the gold standard in the diagnosis of this condition[2,3], but is usually not possible or is delayed due to coagulopathy or ascites. Decisions on termination of pregnancy are usually based on clinical features and basic laboratory parameters. Diagnostic criteria were proposed by Ch'ng et al[4] based on retrospective case series. There was a large prospective study comparing the performance of these 'Swansea criteria' against clinical judgment. This showed considerable agreement between the two methods[5]. The downside of it was the absence of the gold standard diagnostic test – liver biopsy. The accuracy of these criteria in diagnosing biopsy confirmed acute fatty liver of pregnancy has not been studied so far. This is a largest case series till date, correlating clinical findings with biopsy proven acute fatty liver of pregnancy.

In our study, patients in the 3rd trimester of pregnancy who underwent liver biopsy for a probable clinical diagnosis of pregnancy related liver diseases were included. Among them, 76% had histology findings consistent with a diagnosis of acute fatty liver of pregnancy, but 2 patients with micro-vesicular steatosis on liver biopsy, were found later to also test positive for IgM anti-hepatitis E antibody. These findings indicate either a concomitant acute hepatitis E infection (more likely) or the possibility that though liver biopsy is the best available test for acute fatty liver disease, it may not always be diagnostic. The vomiting and anorexia, secondary to acute viral hepatitis may be a precipitating event for AFLP. But for the sake of avoiding confusion, the patients in whom viral markers were not tested were excluded from the analysis, in order to have complete laboratory and clinical details to enable comparison of biopsies with clinical findings.

However, among the 24 patients where the data was complete, there was a considerable overlap in these syndromic diagnoses with 67% patients satisfying clinical criteria for more than one condition (Table 4).

Commonly occurring elements of the criteria, in the study group, for the syndromic diagnosis of acute fatty liver of pregnancy were – jaundice (100%), coagulopathy (96%), elevated transaminases (96%), leucocytosis (87%), altered renal functions (63%) and ultrasound abnormalities (71%) (Table 1). Patients who had diffuse micro-vesicular steatosis (Group A) were similar to the patients with other non-specific findings on liver biopsy (Group B); as far as routine biochemical tests, duration of hospital stay, requirement of blood products and maternal and fetal outcome, were concerned.

Contrary to a recent study by Devarbhavi et al[9], maternal and fetal mortality in our patients was considerably lower (41% and 53% v/s 12% and 29%). S. bilirubin, S. creatinine, total WBC

count or prothrombin time was not significantly different in patients who expired than in others with a favorable outcome. As only 2 patients expired, predictors of mortality could not be studied adequately.

The criteria for diagnosis of AFLP, was fulfilled in 100% patients in group A and also in 1/3rd of patients with defined etiology of liver dysfunction (Group C). The sensitivity and specificity of the diagnostic criteria for acute fatty liver of pregnancy, was 100% and 64% respectively. Negative predictive value was 100%. Considering the high maternal and fetal mortality in this condition, the diagnostic criteria remain relevant despite their low specificity. These criteria have a very high negative predictive value, ensuring no patient with this condition is missed. On the other hand, this may lead to over diagnosis.

There is a high false positive rate, which makes it an inappropriate research tool. The gold standard for diagnosis of acute fatty liver of pregnancy is still the combination of a negative etiology workup and a consistent histology. The use of liver biopsy as a clinical tool for diagnosis may not be needed, as the negative predictive value for the Swansea criteria was 100%.

As the diagnostic criteria for AFLP are satisfied in a proportion of patients with other defined etiology, the use of these criteria in an emergency setting without concomitant diagnostic workup is fraught with a danger of over diagnosis. This may be difficult in a lesser equipped center where the serology tests either may not be available promptly or the processing is delayed[9]. In this group C, the Swansea criteria were helpful in identifying a patient with comparatively severe disease with a consequently higher chance of mortality. Whether these patients benefit from early termination of pregnancy is still debatable.

The retrospective nature of the study and arbitrary derivation of Group C, are the major limitations of the study. Even though this is the largest case series of AFLP from India, the mortality predictors could not be studied, due to small sample size.

A prospective study with detailed clinical, laboratory and histology data will help elucidate the true validity of the clinical diagnostic criteria, but our results on 24 patients indicate that the clinical diagnostic criteria proposed by Ch'ng et al[4], are an accurate and early means to diagnose this dangerous but eminently treatable condition. An early post-partum biopsy may help in confirmation of the diagnosis.

Summary

1. This is the largest study to date, comparing the diagnostic criteria (Swansea criteria) for AFLP against the gold standard – Liver biopsy.

2. Swansea criteria had a sensitivity of 100% and a negative predictive value of 100% in diagnosing AFLP, making it a good clinical test. It excludes the possibility of AFLP.

3. Swansea criteria for AFLP had a poor specificity (64%) and poor positive predictive value rendering it an inadequate test to diagnose AFLP in research setting.

4. In patients with definite other etiology of acute liver failure, Swansea criteria were able to distinguish a sicker patient with higher chance of mortality. Whether these patients will benefit from early termination of pregnancy is still debatable.

5. Mean age of the patients with confirmed AFLP was 23 ± 3 years and the majority -11 (65%) was primigravida. The mean gestational age was 37 weeks (Range 33 – 40 weeks)

6. Jaundice and vomiting were the most common presenting symptoms for AFLP. The presentation was similar in all the groups.

7. The mean MELD of the patients of AFLP was 32.1±6.7. This was similar in all the groups.

8. 12/17 patients with AFLP had an abnormal USG abdomen.

9. Due to a considerable overlap - clinical features, laboratory parameters and radiologic features were not helpful in differentiating AFLP from the patients with other defined etiology.

10. In patients with AFLP, mean stay in hospital was 11 ± 4 days and an average of 18 ± 15 blood products were administered per patient.

11. 9/17 patients with AFLP were delivered by Caesarean section and others by vaginal route.

12. Majority of the babies born to AFLP patients were male (12/17). 3 were twins.

13. 2 (12%) of the mothers and 5 (29%) of the babies had a fatal outcome in patients with AFLP, which was not different from the other groups. Due to small sample size, predictiors of maternal mortality could not be well studied.

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Appendix

Proforma

Name :

IP No. :

Age :

Rural/ Urban :

Religion :

Trimester :

Gravida :

Weeks of pregnancy :

Date of admission :

Date of discharge :

Liver Bx. No. :

Date of liver biopsy :

Symptoms

Duration of symptoms before presentation :

Symptoms at presentation (Jaundice, vomiting etc)

P/H of similar complaints :

F/H of similar complaints :

H/O regular ANC :

Signs

BP :

Fetal distress :

Investigations

LFTs (total bilirubin. Direct bilirubin, S. protein, S. albumin, AST, ALT, ALP)

PT (INR)

aPTT

Fibrinogen

CBC (Hb, TC, DC, Platelets)	S. Creatinine
Plasma Ammonia	Blood sugars
S. Uric acid	S. LDH
HCV antibody	HBsAg
IgM HEV	IgM HAV

p/s MP

Blood C/S	Urine C/S

Urine albumin

USG abdomen :

Liver biopsy findings :

Outcome

Mode of delivery :

Blood products required :

Sex of the child :

Maternal outcome :

Child outcome :